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(54) Therapeutic use of the isopropyl ester derivative of monosialoganglioside in nervous pathologies with an inflammatory component.

(57) The isopropyl ester derivative of ganglioside GM_1 is shown to exhibit antiinflammatory and antiexudative activities, and therefore is useful in the treatment of various systemic, ophthalmic or topical pathologies, particularly those pathologies characterized by inflammatory phenomena. The derivative is also shown to be active after both oral and topical administration.

EP 0 351 784 A2

THERAPEUTIC USE OF THE ISOPROPYL ESTER DERIVATIVE OF MONOSIALOGANGLIOSIDE IN NERVOUS PATHOLOGIES WITH AN INFLAMMATORY COMPONENT

The present invention concerns a new therapeutic application of an ester derivative of GM_1 ganglioside and more precisely of the isopropyl ester of GM_1.

Methods for preparing ester and amide ganglioside derivatives, pharmaceutical compositions containing the functional derivatives, as well as the therapeutic use of these derivatives in therapies for pathologies involving the peripheral nervous system and the central nervous system are known and described in EP Publication 0 167 449.

The present invention concerns the discovery of other valuable properties of a particular ester of GM_1 ganglioside, and more precisely the antiinflammatory and antiexudative properties of the isopropyl ester of GM_1 ganglioside.

Gangliosides are a group of glycosphingolipids with a structure containing a saccharide part bound to a ceramide and a sialic group. The saccharide part is composed of at least one galactose or glucose and of at least one N-acetylglucosamine or N-acetylgalactosamine.

The general structure of a ganglioside can therefore be represented by the following formula:

one sialic acid mole

- one ceramide mole
- at least one galactose or glucose mole
- at least one mole of N-acetylglucosamine or N-acetylgalactosamine

in which these components are bound to glucoside bonds.

Numerous gangliosides have been identified which have proved to be particularly abundant in nerve tissues, especially in those of the brain.

Various studies have shown that the sialic groups most frequently encountered in gangliosides are N-acetylneuraminic acid (NANA) and, to a lesser degree, N-glycolylneuraminic acid. Among the many identified gangliosides, considerable amounts of the following gangliosides, classified by their international symbols, have been found in mixtures obtained from bovine brain tissue:

GD_{1b} (16%)

$$Gal(1\xrightarrow{\beta}3)GalNAC(1\xrightarrow{\beta}4)Gal(1\xrightarrow{\beta}4)Glc(1\xrightarrow{\beta}1)Ceramide$$

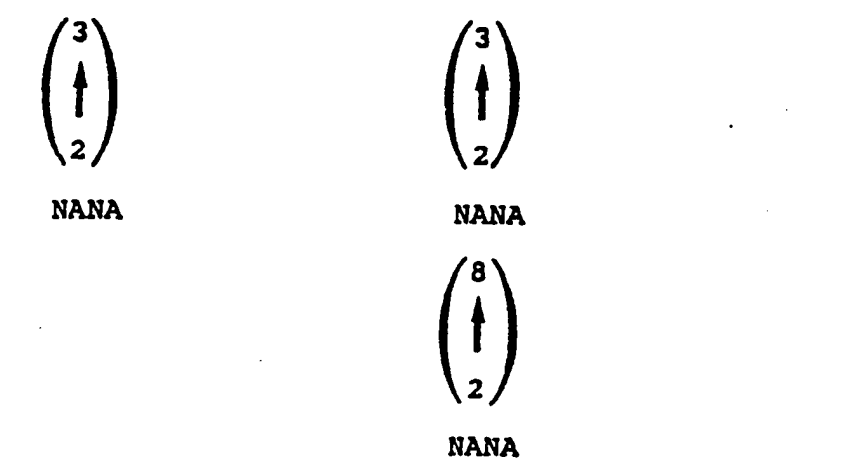
$$\begin{pmatrix} 3 \\ \uparrow \\ 2 \end{pmatrix}$$

NANA

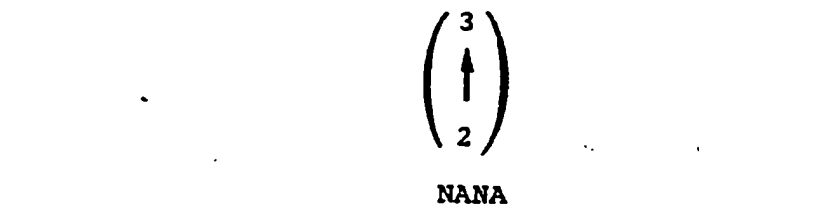
$$\begin{pmatrix} 8 \\ \uparrow \\ 2 \end{pmatrix}$$

NANA

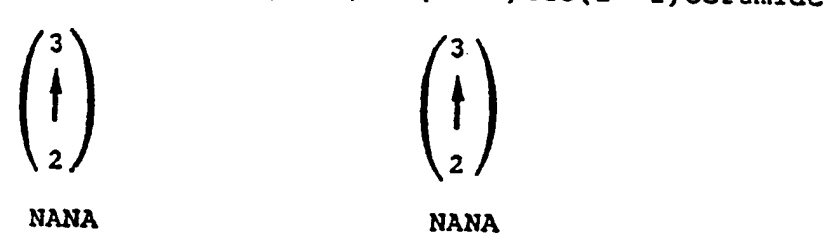
GT_{1b} (19%)



GM_1 (21%)

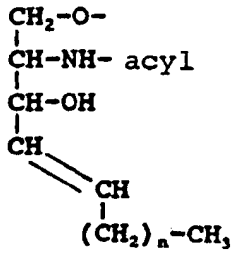


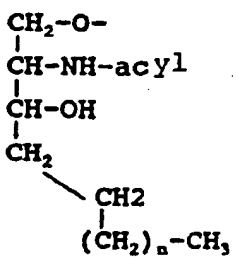
GD_{1a} (40%)



where Glc stands for glucose, GalNAc stands for N-acetylgalactosamine, Gal stands for galactose, NANA stands for N-acetylneuraminic acid and the percentages shown in brackets indicate the quantities relative to each ganglioside found in a ganglioside mixture extracted from bovine brain tissue.

The individual gangliosides reported above, isolated from a mixture extracted from animal tissues and considered to be quite "pure", still comprise mixtures due not only to the variability of their ceramide part, which corresponds to one of the formulae

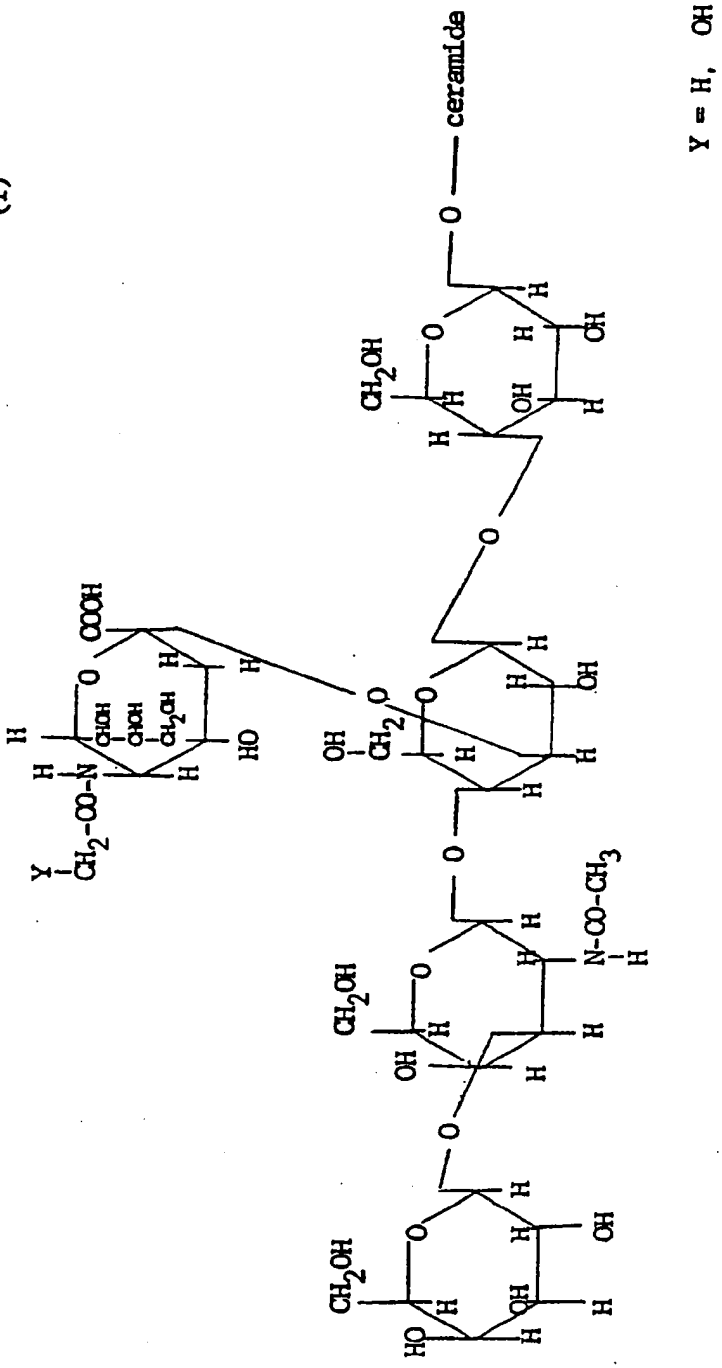




in which n = 10-16 and the acyl may derive from a saturated or unsaturated fatty acid having between 17 and 24 carbon atoms or from a corresponding hydroxy acid, but also to the variability of sialic acid, which may be either N-acetylneuraminic acid or N-glycolylneuraminic acid.

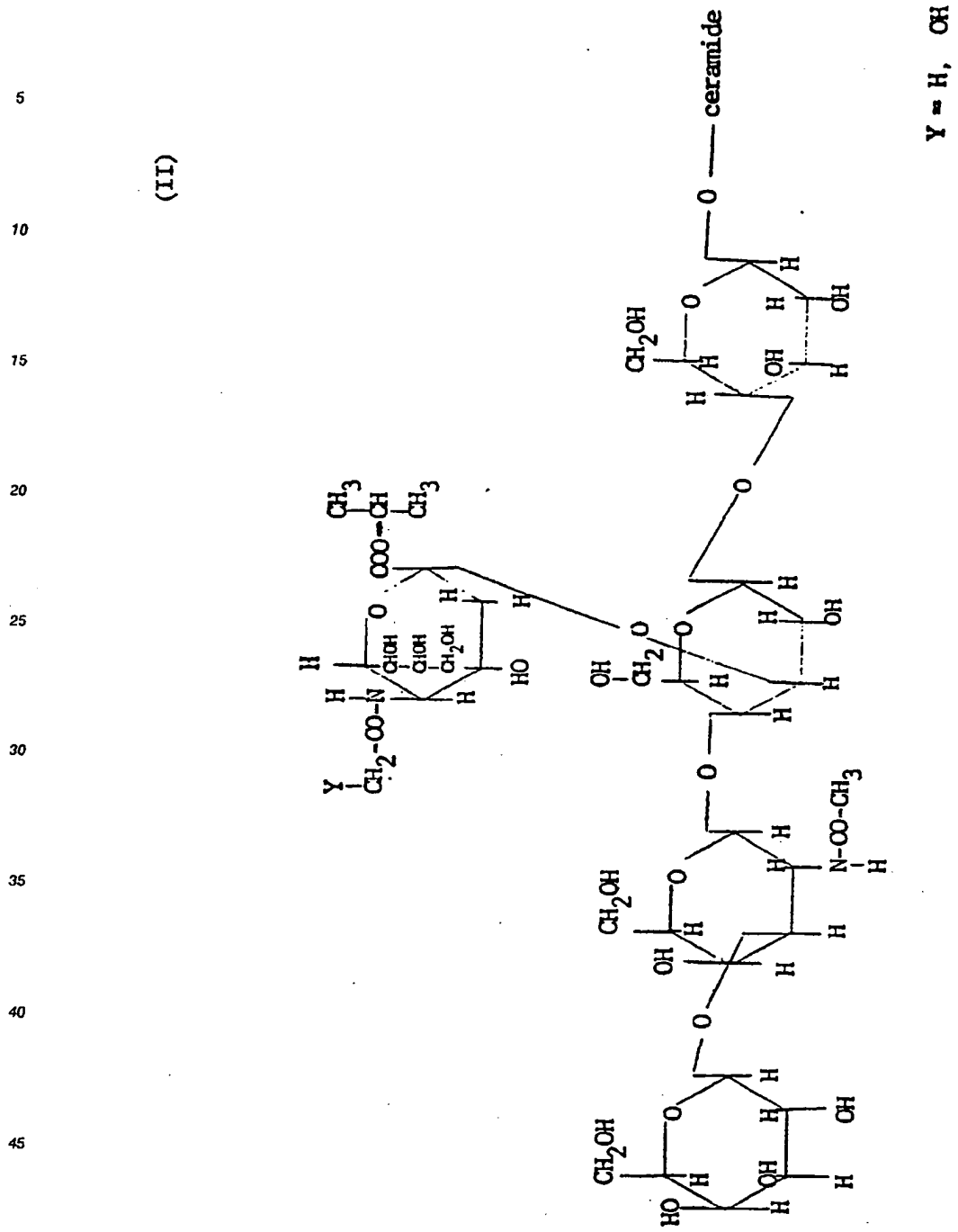
GM_1 ganglioside, whose isopropyl ester is the basis of the present invention, therefore represents also a mixture of compounds of the formula

(I)



where "ceramide" represents a group of residues of the above formulae.

The isopropyl ester of GM_1 can, therefore be represented by the following formula:



It is known that gangliosides play an important role in the nervous system and it has recently been demonstrated that gangliosides are useful in therapies for peripheral nervous system pathologies and in pathologies of the central nervous system.

The therapeutic action of gangliosides seems to consist above all in stimulating sprouting phenomena of the nerve cell and in activating the membrane enzymes involved in the conduction of nervous stimuli, such as the enzyme (NA^+,K^+)ATPase. Neuronal sprouting stimulated by gangliosides enhances functional recovery of damaged nerve tissue, both central and peripheral.

It is also known that gangliosides, both in mixture and as single fractions, have a specific and high level of antinociceptive activity: they are effective in reducing writhings induced by phenylquinone and acetic acid

and increased permeability induced by acetic acid, see EP 0 183 572.

In subsequent studies it has been demonstrated that a group of amides and esters of gangliosides have an advantage over gangliosides themselves in remaining active for a longer period of time ("retard" effect) and having more selective activity EP 0 167 449; Arch. Int. Pharmacodyn. 291, 238-252 (1988). It has now been observed that, apart from their antinociceptive action, ganglioside esters also present an antiinflammatory action which is quite dissociated from the first. Further studies described herein have brought to light valuable antiexudative and antiinflammatory properties of the isopropyl ester of GM_1 monosialoganglioside. The remarkable advantage of this ester is that while it can be administered orally, it is also active after topical administration.

Method of Preparation

As noted above, EP 0 167 449 describes methods for the preparation of ganglioside ester derivatives, including a procedure utilizing an internal ganglioside ester which is subsequently esterified with an alcohol. The GM_1 isopropyl ester is preferably prepared according to this procedure. However, other methods of obtaining the isopropyl ester may be based upon known esterification methods, such as alkylation reaction by means of isopropyl halogens in aprotic solvents or in mixtures of aprotic solvent, esterification by means of acidic catalysis and finally esterification catalyzed by ionic exchange resin.

The following, therefore, is an example of the preparation of the GM_1 isopropyl ester utilizing the internal ester process.

Preparation Example 1: Preparation of Isopropyl ester of GM1

5 g of the internal ester of the ganglioside GM_1 (3.27 mM) are dissolved in 200 ml of an anhydrous mixture of methylene chloride and isopropyl alcohol 4:1. 176 mg (3.27 mM) of sodium isopropylate dissolved in 50 ml of anhydrous methanol are added and the mixture is refluxed for 2 hours. At the end of the reaction the mixture is neutralized with Dowex AG 50x8 anhydrous resin (H^+ form), the resin is separated by filtration and washed with isopropyl alcohol and the solution is evaporated by drying. The residue is gathered in 50 ml of methylene chloride/isopropanol 1:1 and the reaction product is precipitated by pouring it into 250 ml of acetone. The raw product (4.9g) is purified by preparative high pressure chromatography with 60 H Merck silica gel, using as solvent a mixture of chloroform/methanol/isopropanol/ammonium carbonate at 2% 1140:820:180:140. The pure fractions are gathered, evaporated by drying, redissolved in 15 ml of chloroform/methanol 1:1 and the product is precipitated with 75 ml of acetone. This product represents the isopropyl ester of the ganglioside GM_1. Yield 4.9g.

IR spectroscopy carried out on KBr pellets shows the typical bond of the ester at 1750 cm^{-1}. Chromatography on silica gel plates with chloroform/methanol/$CaCl_2$ at 0.3% 55:45:10 and determined with Ehrlich reagent shows the product to be a unitary compound with an Rf of 0.85 and free from the internal ester used as starting product (Rf 0.75) and from the ganglioside GM_1 (Rf 0.65). By treatment with an 0.1N solution of Na_2CO_3 for 60° for an hour, the ester bond is split, giving the primary product, GM_1.

Therapeutic Use

The isopropyl ester of GM_1 ganglioside, as described in the above noted EP 0 167 449, is useful in therapies for peripheral nervous system pathologies of traumatic, compressive, degenerative or toxic infective origin, based upon the stimulation of nervous regeneration and neuromuscular functional recovery; and in pathologies of traumatic, anoxic,, degenerative or toxic infective origin in the central nervous system based upon stimulation of neuronal sprouting phenomena for functional recovery. It has now been found according to the present invention that the GM_1 isopropyl ester derivative may be used, due to its valuable anti-exudative and antiinflammatory properties, in systemic, ophthalmic and topical pathologies.

In the field of ophthalmology, the isopropyl ester derivative of GM_1 can be used in pathologies of diverse etiopathogenesis in which inflammatory phenomena are present and marked, such as: blepharitis, conjunctivitis, keratoconjunctivitis, keratitis, episcleritis, anterior, intermediate and posterior uveitis, sympathetic ophthalmia, retinitis, retinal vasculitis, optic and retrobulbar neuritis,, dysthyroid ophthalmopathy, and in post-surgical treatments following surgical operations to the bulbus oculi and annexa oculi.

For topical use, the isopropyl ester derivative of GM_1 is useful in pathologies of a nervous nature with an inflammatory component, such as lumbago, lumbo-sciatica, cervicobrachialgia in the various herpetic manifestations and infections such as herpes zoster.

This ganglioside derivative, like GM_1, has the important advantage of being administrable by oral route and of being remarkably efficacious by this route. Like GM_1, the ganglioside derivative can be used by topical route.

The isopropyl ester of GM_1 according to the present invention can be used as a drug in pharmaceutical preparations for administration to man or animal by oral, intramuscular, intravenous, subcutaneous or intradermal, topical, ophthalmic routes, by means of tablets, capsules, injections or intravenous infusions, gels, creams, ointments and eye drops. The preparations intended for oral administration can be prepared as powders or freeze-dried products mixed with one or more pharmaceutically acceptable excipients in the form of tablets or capsules. The preparations intended for administration as injections can be prepared as powders or freeze-dried products mixed with pharmaceutically acceptable excipients or diluents and contained in buffered solutions with a suitable pH and osmolarity compatible with the physiological fluids. The preparations intended for topical applications can be prepared as powders or freeze-dried products, mixed with one or more pharmacologically suitable excipients or vehicles and capable of permitting penetration of the active principle in the form of gels, creams, ointments. The preparations intended for ophthalmic administration can be prepared as powders or freeze-dried products mixed with one or more pharmaceutically acceptable excipients or diluents and contained in buffered solutions with suitable pH and osmolarity compatible with the ocular system.

The dosage to be administered depends on the desired effect and on the chosen administration route. As an example (not limitative) the dosage can be between 0.05 and 5 mg of active substance per kg of body weight/day with a unitary posology of between 0.05 and 2 mg/kg of body weight.

The following tables describe pharmaceutical compositions useful in the invention.

The types of pharmaceutical preparation shown in Table 1 are administrable by oral route and are represented by examples of tablets and capsules.

Example 1 describes a tablet obtained by direct compression of the components.

Example 3 describes a tablet obtained by damp granulation and subsequent compression.

Examples 2 and 4 report gastroresistant tablets.

Example 5 reports a capsule in hard gelatin.

Table 1 - Examples of pharmaceutical preparations for oral administration

Example 1

-	active substance	mg	25
-	microcrystalline cellulose	mg	100
-	lactose	mg	20
-	maize starch	mg	10
-	talcum	mg	5
-	magnesium stearate	mg	1.5

Example 2

Tablet described in Example 1 with a coating composed of:

-	acetophthalate cellulose	mg	4
-	hydroxypropylmethylcellulose	mg	0.2
-	diethylphthalate	mg	1.4
-	shellac	mg	1.5

Example 3

-	active substance	mg	50
-	lactose	mg	80
-	maize starch	mg	50
-	talcum	mg	3
-	magnesium stearate	mg	1.2

Example 4

Tablet described in Example 3 with a coating composed of:

-	acetophthalate cellulose	mg	4
-	hydroxypropylmethylcellulose	mg	0.2
-	diethylphthalate	mg	1.4
-	shellac	mg	1.5

Example 5

Granules comprising:

-	active substance	mg	50
-	lactose	mg	80
-	maize starch	mg	50
-	talcum	mg	3

- magnesium stearate mg 1.2

Hard gelatin involucre (Parke-Davis, etc.)

The type of pharmaceutical preparations shown in Table 2 are used for intramuscular, subcutaneous, intradermal or intravenous administration.

Table 2

Examples of pharmaceutical preparations:			
Example 1			
-	active substance	mg	25
-	sodium chloride	mg	16
-	phosphate buffer in distilled water q.b.	ml	2
Example 2			
-	active substance	mg	50
-	mannitol	mg	80
-	phosphate buffer in distilled water q.b.	ml	2

The type of pharmaceutical formulations shown in Table 3 relate to formulations to be used by topical route.

Example 1 describes an aqueous gel.
Example 2 describes a cream.
Example 3 describes an ointment.

Table 3

Examples of pharmaceutical preparations (topical)		
Example 1		
-	active principle	1%
-	carbopol 940	1%
-	glycerol	3%
-	methyl paraben	0.2%
-	propyl paraben	0.02%
-	purified H_2O q.b.	100 gr
Example 2		
-	active principle	1%
-	monostearate sorbitan	1.5%
-	(2) OE monostearate sorbitan	2.5%
-	vaseline oil	5%
-	glycerol	3%
-	methyl paraben	0.2%
-	propyl paraben	0.02%
-	purified H_2O q.b.	100 gr
Example 3		
-	active principle	1%
-	white wax	7%
-	spermaceti	8%
-	sweet almond oil	60%
-	purified H_2O q.b.	100 gr

Table 4 reports examples of pharmaceutical formulations to be used by ophthalmic route in the form of eye drops.

Table 4

Examples of pharmaceutical preparations		
Example 1		
-	active principle	0.5%
-	NaCl	0.85%
-	phosphate buffer in distilled water q.b.	100 ml
Example 2		
-	active principle	1%
-	NaCl	0.85%
-	phosphate buffer in distilled water q.b.	100 ml

Pharmacological Properties

The above mentioned patent publication EP 0 167 449 describes ester derivatives of gangliosides, methods of producing such derivatives and their efficacy in therapies for nervous system pathologies. Ester derivatives of gangliosides may be used to treat a range of nervous disorders including pathologies of the

peripheral and central nervous systems following disease or trauma. These substances may also be used in post-surgical therapies after operations involving motor and sensory nerves such as slipped disc operations.

One publication (Arch. Int. Pharmacodyn. 272, 103-117, (1984)) reports the antinociceptive properties of a ganglioside mixture which is able, after subcutaneous administration, to reduce the number of phenylquinone-induced writhings (and acetic acid-induced writhings) as well as increased permeability induced by acetic acid.

It has now been observed that the esterification of a ganglioside, particularly esterification of GM_1 with isopropyl alcohol, induces a dissociation of its antinociceptive and antiinflammatory properties. Indeed, the new derivative, isopropyl ester of GM_1, has a strong inhibiting effect on exudative and inflammatory reactions. It inhibits in a dose-dependent manner acetic acid-induced peritonitis, edema induced by carrageenan, serotonin, histamine and bradykinin in rat paw.

Its antiinflammatory activity is limited to a certain dose range only, suggesting an action mechanism of considerable interest.

In terms of the molar ratio, the isopropyl ester of GM_1 ganglioside is more active than the commercially available comparison drug.

Its antiedematous effect develops over a period of 30-60 minutes after induction of edema and reaches a peak within the first few hours, suggesting that mediators such as histamine, serotonin and bradykinin are involved in the process.

Apart from the systemic route (os, i.p., s.c.) the isopropyl ester derivative of GM_1 ganglioside presents antiexudative and antiinflammatory activity following topical application to the paw. After topical application to the paw, the new derivative proves to have an antiexudative activity; therefore, a certain systemic absorption is hypothesized.

In the case of GM_1 too, it is possible to observe antiexudative and antiinflammatory activities, although these activities do not reach the high percentages of inhibition reached by the isopropyl ester derivative.

The antiexudative and antiinflammatory activities comprising the object of the present invention can be evaluated by means of the following tests:

ANTIEXUDATIVE ACTIVITY EVALUATED BY MEANS OF THE ACETIC ACID-INDUCED PERITONITIS TEST

Procedure:

The study was conducted on Sprague-Dawley rats, weighing between 200 and 300 gr.

An evaluation was made of the capacity of the isopropyl ester of GM_1 ganglioside (hereafter known as AGF_{44}) and GM_1 itself, to inhibit the formation of peritoneal exudate following intraperitoneal injection (10 ml/kg) of a 0.5% acetic acid solution.

To study administration by oral, subcutaneous and intraperitoneal routes, AGF_{44} and GM_1 (solubilized in 10 ml/kg of sterile saline physiological solution) and a comparison compound indomethacin were administered by the individual routes one hour before the injection of acetic acid.

To study topical administration, one hour before i.p. injection of acetic acid, AGF_{44} and GM_1 in the form of 0.1% aqueous gels and the comparison 5% Artrosilene gel (ketoprofen lysine salt) were applied to the right paws with a light massage for 30 seconds to ensure complete absorption of the gel.

The control groups received saline physiological solution (10 ml/kg) and placebo gel (0.2 ml/rat), respectively. 30 minutes after exudate inducement the animals were sacrificed, samples were taken of the peritoneal exudate and the percentage of inhibition of the same in relation to control values was calculated.

Results:

The results are reported in Table 5. It is easy to see from the data presented, that AGF_{44} has a remarkable dose-dependent antiexudative efficacy. The product proves to be particularly active at doses of between 1 and 5 mg/kg, but it is also efficacious at doses of less than 0.1 mg/kg (in the order of 0.1 mg/kg). At doses of over 10 mg/kg the activity decreases.

Peritoneal exudate inhibition is particularly strong after oral administration, when values of between 70-80% of inhibition are obtained. At 1 mg/kg the activity is comparable to that of indomethacin. After subcutaneous and intraperitoneal treatment, the anti-exudative effect is evident, even though the inhibition

values reached are slightly inferior (50-60%). Further interest in this compound derives from analysis of the results of topical treatment where an antiexudative activity is present also when AGF_{44} is applied to the paw in the form of an aqueous gel. It is hypothesized that these results suggest a certain systemic absorption is hypothesized. In the same way, GM_1 presents a marked antiexudative activity by all the administration routes tested, above all in the case of oral administration, without however, reaching the high percentages of inhibition reached by the isopropyl ester.

Table 5:

Results of the acetic acid-induced peritonitis test in rat, using an i.p. injection (10 ml/kg) of a solution of 0.5% acetic acid.

Treatment	dose (mg/kg)	No. animals	% inhibition
Oral			
Controls (saline phys. solution 10 ml/kg)	-	60	-
GM_1 isopropyl ester	1	12	70
GM_1 isopropyl ester	2.5	12	72
GM_1 isopropyl ester	5	12	77
GM_1	1	12	56
GM_1	2.5	12	63
Indomethacin	1	12	74
Indomethacin	2.5	12	90
Subcutaneous			
Controls (saline phys. solution 10 ml/kg)	-	60	-
GM_1 isopropyl ester	1	12	47
GM_1 isopropyl ester	2.5	12	61
GM_1 isopropyl ester	5	12	70
GM_1	1	12	44
GM_1	2.5	12	52
Indomethacin	1	12	64
Indomethacin	2.5	12	84

Table 5 (cont'd)

Treatment	dose (mg/kg)	No. animals	% inhibition
Intraperitoneal			
Controls (saline phys. solution 10 ml/kg)	-	60	-
GM_1 isopropyl ester	1	12	55
GM_1 isopropyl ester	2.5	12	60
GM_1 isopropyl ester	5	12	64
GM_1	1	12	47
GM_1	2.5	12	51
Indomethacin	1	12	70
Topical			
Controls (placebo gel 0.2 ml/rat)	-	40	-
GM_1 isopropyl ester 0.1% gel (0.2 ml/rat)	1.4	20	43
GM_1 0.1% gel (0.2 ml/rat)	1.4	20	30
Artrosilene 5% gel 0.4 ml/rat)	70*	20	40

* dose expressed as ketoprofen acid

ANTIEDEMATOUS ACTIVITY EVALUATED BY THE CARRAGEENAN-INDUCED EDEMA TEST IN THE PAW

Procedure:

The study was conducted on male Sprague Dawley rats, weighing about 160 ± 10 gr.
An evaluation was made of the activity of the isopropyl ester of GM_1 ganglioside (AGF_{44}) and GM_1 in

inhibiting the formation of edema following injection of a sterile aqueous solution of 1% carrageenan into the plantar aponeurosis of the right hand paw (0.1 ml/rat).

To study administration by oral, subcutaneous and intraparitoneal routes, AGF_{44} and GM_1 (solubilized in 10 ml/kg of sterile saline physiological solution) were compared to indomethacin as a comparison compound. For study of the oral route, each compound was administered by oral route one hour before injection of carrageenan. For study of the subcutaneous and intraperitoneal routes, each compound was administered 30 minutes before the same. To study topical administration, AGF_{44} and GM_1 (as 0.1% aqueous gels) were compared to 5% Artrosilene gel (ketoprefene lysine salt). Each compound was applied locally to the right paw, and administration was effected twice, one hour before and immediately after injection of carrageenan, massaging lightly for 30 seconds to ensure complete absorption.

The control groups received saline physiological solution (10 ml/kg) and placebo gel (0.2-0.4 ml/rat twice) respectively.

Plethysmometric evaluation of the volume of the right paw was effected immediately before sub-plantar injection of carrageenan an 3 hours after the same. The antiedematous effect of the treatment was calculated by evaluating the average increase in paw volume at the 3rd hour (compared to time 0) based on control values.

Results:

The results are reported in Table 6.

Table 6:

Results of the carrageenan-induced edema test by means of injection into the plantar aponeurosis of the right hind paw of a sterile aqueous solution of 1% carrageenan (0.1 ml/rat).

Treatment	dose (mg/kg)	No. animals	% inhibition
Oral			
Controls (saline phys. solution 10 ml/kg)	-	60	-
GM_1 isopropyl ester	1	12	20
GM_1 isopropyl ester	2	12	32
GM_1 isopropyl ester	5	12	60
GM_1	2	12	20
GM_1	5	12	32
Indomethacin	1	12	22
Indomethacin	5	12	67
Intraperitoneal			
Controls (saline phys. solution 10 ml/kg)	-	60	-
GM_1 isopropyl ester	1	12	18
GM_1 isopropyl ester	2	12	32
GM_1 isopropyl ester	5	12	57
GM_1	2	12	20
GM_1	5	12	30
Indomethacin	1	12	23
Indomethacin	5	12	67

Table 6 (cont'd)

Treatment	dose (mg/kg)	No. animals	% inhibition
Subcutaneous			
Controls (saline phys. solution 10 ml/kg)	-	60	-
GM_1 isopropyl ester	1	12	25
GM_1 isopropyl ester	2	12	30
GM_1 isopropyl ester	5	12	50
GM_1	2	12	19
GM_1	5	12	31
Indomethacin	1	12	30
Indomethacin	5	12	60
Topical			
Controls (placebo gel 0.2 ml/rat)	-	40	-
Controls (placebo gel 0.4 ml/rat)	-	40	-
GM_1 isopropyl ester 0.1% gel (0.2 ml/rat/twice)	1.25 x 2	12	32
GM_1 isopropyl ester 0.1% gel (0.4 ml/rat/twice)	2.5 x 2	12	43
GM_1 0.1% gel (0.2 ml/rat/twice)		12	20
Artrosilene 5% gel 0.2 ml/rat/twice)	70*	12	38

* dose expressed as ketoprofen acid

The efficacy of AGF_{44} in inhibiting carrageenan-induced edema in the paw is evident, although in this test it does not reach such high percentages of inhibition as in the acetic acid-induced peritonitis test. Its antiinflammatory activity is effective at low doses (it diminishes at doses of over 10 mg/kg), and develops within the first few hours after edema inducement, suggesting that the antiinflammatory activity is aimed at effects related to histamine,, serotonin and bradykinin release following damage.

In the carrageenan-induced edema test, AGF_{44} is active by all administration routes tested: oral,

subcutaneous, intraperitoneal, topical. Maximum efficacy is reached by oral route (50-60% inhibition). Of great interest were the results obtained from topical treatment, because in that test AGF_{44} applied to the paw has an antiedematous activity even at the lowest dose tested.

In the case of GM_1 too, an antiedematous activity is present by the the various administration routes tested. The efficacy, however, is inferior to that observed for the ester derivative.

Claims

1. Use of the isopropyl ester of GM_1 ganglioside for the manufacture of a medicament with an antiinflammatory and antiexudative action.

2. Use of the isopropyl ester of GM_1 ganglioside according to claim 1 for the manufacture of a medicament for the treatment of systemic, ophthalmic or topical pathologies.

3. Use of the isopropyl ester of GM_1 ganglioside according to one of claims 1 or 2 for the manufacture of an ophthalmic medicament for the treatment of ophthalmological pathologies characterized by marked inflammatory phenomena.

4. Use of the isopropyl ester of GM_1 ganglioside according to claim 3 for the manufacture of a medicament for the treatment of blepharitis, conjunctivitis, keratoconjunctivitis, keratitis, episcleritis, anterior, intermediate and posterior uveitis, sympathetic ophthalmia, retinitis, retinal vasculitis, optic and retrobulbar neuritis, dysthyroid ophthalmopathy and for postoperative treatments following surgical operations to the bulb and appendages.

5. Use of the isopropyl ester of GM_1 ganglioside according to one of claims 1 or 2 for the manufacture of a topical medicament for the treatment of nervous pathologies characterized by an inflammatory component.

6. Use of the isopropyl ester of GM_1 ganglioside according to claim 5 for the manufacture of a medicament for the treatment of lumbago, lumbosciatica, cervicobrachialgia and herpes zoster.

7. Use of the isopropyl ester of GM_1 ganglioside according to one of claims 1-3 for the manufacture of a medicament for oral administration.

8. Use of the isopropyl ester of GM_1 ganglioside according to one of claims 4 or 5 for the manufacture of a medicament for topical administration.

9. A pharmaceutical composition which comprises an effective antiinflammatory or antiexudative amount of the isopropyl ester of GM_1 ganglioside, and a pharmaceutically acceptable carrier, diluent or excipient.

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(54) Therapeutic use of the isopropyl ester derivative of monosialoganglioside in nervous pathologies with an inflammatory component.

(57) The isopropyl ester derivative of ganglioside GM_1 is shown to exhibit antiinflammatory and antiexudative activities, and therefore is useful in the treatment of various systemic, ophthalmic or topical pathologies, particularly those pathologies characterized by inflammatory phenomena. The derivative is also shown to be active after both oral and topical administration.

EP 0 351 784 A3

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PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application number
EP 89 11 3160

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D,X	EP-A-0 167 449 (FIDIA SpA) * Page 6, second paragraph; page 33, example 6; page 77, last paragraph - page 78, first paragraph; page 82, last paragraph - page 84, line 2; pages 92,93; claims 15,16 * --	1-9	A 61 K 31/70
D,A	ARCH. INT. PHARMACODYN, vol. 291, January-February 1988, pages 238-252; M. AMICO-ROXAS et al.: "Characterization of the antinociceptive effects of a ganglioside derivative in rodents" * The whole article * --	1-9	TECHNICAL FIELDS SEARCHED (Int. Cl.4) A 61 K C 07 H
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INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 4,6-9
Claims searched incompletely: 1-3,5
Claims not searched:
Reason for the limitation of the search:

Claims 1-3 and 5 do not make completly clear which specific therapeutic use is meant. The search gas been restricted to the diseases mentioned in claims 4 and 6. (See Official Journal EPO 3/1985, pages 64-70 and EPC, art. 84)

Place of search	Date of completion of the search	Examiner
THE HAGUE	18-09-1990	ORVIZ DIAZ

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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EP 89 11 3160

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	KLIN. MOL. AUGENHEILK., vol. 180, no. 5, 1982, pages 493-496, F. Enke Verlag, Stuttgart, DE; B. ALGAN et al.:"Les gangliosides (Cronassial) dans le traitement des neuropathies oculaires. Premiers résultats" * The whole article *	1-9	
A	ACTA NEUROPATHOL., vol. 62, nos. 1-2, 1983, pages 45-50, Springer-Verlag 1983; F. NORIDO et al.: "Monosialoganglioside (GM_1) treatment of Ouabain-induced retinopathy in the rabbit" * The whole article *	1-9	TECHNICAL FIELDS SEARCHED (Int. Cl.4)

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